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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	GHDX-005	5745

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66 and 68-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66 and 68-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed August 31, 2010. This action is made FINAL.

Claims 66, 68-81 are currently pending.

Claims 66 has been amended.

Claim Rejections - 35 USC § 112 1st paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified based on the claim amendments:

Claims 66 and 68-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention/ Scope of the Claims:

Claim 66 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with cetuximab. Claim 66 comprises (a) assaying a normalized level of a predictive RNA transcript in a sample comprising ErbB 1 expressing colon cancer cells obtained from said patient, wherein the predictive RNA transcript is the transcript of laminin gamma 2 (LAMC2); (b) analyzing the normalized level of the LAMC2 transcript; and (c) predicting the likelihood of response of the patient to treatment with cetuximab by comparing the normalized level of the LAMC2 transcript to gene expression data obtained from reference samples derived from patients with colong cancer. The wherein clause states that an increased normalized level of LAMC2 RNA transcript correlates with a decreased likelihood of response to treatment with cetuximab. Thus the nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with cetuximab.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several ErbB1 inhibitors are promising drug candidates for the treatment of ErbB1 expressing cancers. In particular the specification (page 26) teaches that cetuximab is a monoclonal antibody that blocks the

ErbB1 and ErbB1 -dependent cell growth that is currently being tested in phase III clinical trials.

The specification teaches (Example 2) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Following treatment with an unspecified EGFR inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease.

Table 3 shows the results obtained using the partial response criterion. LAMC2, was found to be over expressed. LAMC2 was also found to have a negative response ($p=0.0357$). Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with the EGFR inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to EGFR inhibitor (page 28).

In the instant case the specification does not teach which EGFR inhibitors were used in example 2. However it is noted for the record that on April 17, 2008 the Applicants have submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these ErbB1 inhibitors. Then on December 3, 2009 the Applicants submitted two more declarations by Joffre B. Baker, PhD and Steve Shak M.D. stating that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy.

The declaration further states that the three partial responders were treated with EMD72000 alone.

Thus the data presented in Table 3 is based on 15 patients treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. As stated above three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Since the three partial responders were treated with EMD72000, the patients treated with cetuximab must have either had stable disease or progressive disease.

State of the Art and the Unpredictability of the Art:

The level of skill in the art is deemed to be high. However the unpredictability with regard to correlating the level of LAMC2 with a patient's response to treatment with cetuximab is even higher.

In the instant case it is highly unpredictable if one can predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab. For example the declaration filed by Steven Shak MD filed on May 25, 2010 refers to a graph showing the LAMC2 mRNA level for each of the 23 patients (See Exhibit 1). The graph does not indicate which of the patients received EMD 72000 and which patients received cetuximab however the graph does differentiate between the non partial responders (No PR) and the partial responders (Yes PR). Each circle represents a patient. As shown in Exhibit 1 the 3 partial responders had LAMC2 values ranging between approximately 3.1-5.25 whereas the 20 non responders had LAMC2 values ranging between approximately 3.2-7.5. Here it is noted that there is substantial

overlap between the two groups. In fact 12 of the 18 non responders had LAMC2 values that fell within the 3.1-5.25 range. Based on this information it does not appear that one of skill in the art could accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with cetuximab since 12 of the non responders would have been predicted to respond based on their LAMC2 levels.

Further it is noted that based on the declarations filed we do know that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. We also known that the three partial responders were treated with EMD72000. Since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. The finding that the three patients who responded to EMD 72000 had lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease does not necessarily mean that patient who respond cetuximab will also have lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease. This unpredictability is discussed in a post filing date paper by Solmi et al (BMC Cancer 2008 Vol 8 page 227). Solmi teaches that they characterized HT-29 and Caco-2 human colon cancer cell lines untreated and treated with cetuximab or gefitinib alone and in combination with EGF. Solmi teaches that cetuximab has opposite effects on gene expression profiling compared to EGF alone or gefitinib, indicating a different action mechanism than the other drug, even though the cell cyto-morphological

transformations are sometimes the same, possibly suggesting an important role by translational regulation on the cellular pathways (page 3). As such Solmi teaches that treatment with different EGFR inhibitors results in different gene expression patterns and therefore the findings with one drug can not be extrapolated to another drug.

Regarding the statistically significant p-value for LAMC2 presented in Table 3 it is noted that the p value is based on the data combined from 23 patients that were treated with two different drugs. The p value was not based on treatment with cetuximab alone and it is unclear how the p-value would change if the data from the 15 patients that were treated with EMB 72000 were removed.

Quantity of Experimentation:

The specification asserts that patients diagnosed with colon cancer with elevated levels of LAMC2 are less likely to respond to a treatment with cetuximab. However since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. Based on the data presented in the specification and the declarations that have been filed it is unpredictable if the claimed method works as such further experimentation would be required. For example, such experimentation may involve treating a large number of colon cancer patient's cetuximab, assaying the expression levels of LAMC2, and then monitoring the patients to determine disease progression. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Arguments

3. In the response filed on August 31, 2010 the Applicants traversed the enablement rejection.

The response states that Applicants have amended claim 66 to recite "predicting the liklihood of response of the patient to treatment with cetuximab by comparing the normalized level of the LAMC2 transcript to gene expression data obtained from reference samples derived from patients with colon cancer, wherein an increased normalized level of LAMC2 RNA transcript correlates with a decreased likelihood of response to treatment with cetuximab". The amendment has been fully considered and the portions of the enablement rejection that address that (a) the claims do not define what the increase is in comparison to and (b) the claims do not indicate how the increased level of LAMC2 RNA correlates with resistance to treatment with cetuximab, have been withdrawn.

The response states that claims 82 and 83 have been cancelled. The amendment has been fully considered and the portions of the enablement rejection that

address the fact that several of the genes listed in claims 82 and 83 did not have statistically signfiicant p values, have been withdrawn.

The response asserts that the claimed invention is fully enabled by the specification. The Applicants argue that while the data in Table 3 is based on three responders treated with the EGFR inhibitor EMD 72000, the specification teaches that "the finding of the present invention are equally applicable to other EGFR inhibitors, including without limitation, and EFGR antibodies" (page 26). The specification discloses cetuximab, a monoclonal antibody that blocks the EGFR and EGFR depending cell growth, as an example of an EGFR inhibitor (page 26). This argument has been fully considered but is not persuassive. The specification makes the assertion that the findings of the present invention would be applicable to other EGFR inhibitors however the specification does not provide any evidnece which supports this assertion. Since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. The fact that the three patients who responded to EMD 72000 had lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease does not necessarily mean that patients who respond to cetuximab will also have lower levels of LAMC2 RNA compared to patients who did not respond or had progressive disease. The post filing date art of Solmi et al (BMC Cancer 2008 Vol 8 page 227) establishes that treatment with different EGFR inhibitors results in different gene expression patterns. Solmi teaches that they characterized HT-29 and Caco-2 human colon cancer cell lines untreated and treated with cetuximab or gefitinib

alone and in combination with EGF. Solmi teaches that cetuximab has opposite effects on gene expression profiling compared to EGF alone or gefitinib, indicating a different action mechanism than the other drug, even though the cell cyto-morphological transformations are sometimes the same, possibly suggesting an important role by translational regulation on the cellular pathways (page 3). As such Solmi teaches that treatment with different EGFR inhibitors results in different gene expression patterns and therefore the findings with one drug can not be extrapolated to another drug. As such Applicants have not provided conclusive or convincing evidence to one skilled in the art that the findings of the present invention would be applicable to other EGFR inhibitors.

As additional evidence that the findings in the instant application are indeed equally applicable to cetuximab the Applicants submit that PG PUB 2009/0298701 reports on the analysis of gene products from tumors obtained from patients that had undergone cetuximab treatment for colon cancer. This argument has been fully considered but is not persuasive. The PG Pub that Applicants are attempting to rely upon as evidence that the claims are enabled is their own post filing work. Applicants are reminded that "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are

probative. MPEP 716.02. This should not be construed as an invitation to file a declaration after final. Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted: (1) prior to a final rejection,(2) before appeal in an application not having a final rejection, or (3) after final rejection and submitted (i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or (ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or (iii) under 37 CFR 1.129(a).

Finally the Applicants assert that as first disclosed in the instant application and further shown in the '701 publication the claimed invention is not unpredictable and does not require undue experimentation. This argument has been fully considered but is not persuasive. Regarding the instant specification since none of the patients that were given cetuximab responded to treatment we do not know what the expression level of LAMC2 would be in a patient that responded to treatment with cetuximab. Based on the data presented in the specification and the declarations that have been filed it is unpredictable if the claimed method works as such further experimentation would be required. For example, such experimentation may involve treating a large number of colon cancer patient's cetuximab, assaying the expression levels of LAMC2, and then monitoring the patients to determine disease progression. As such at the time of the filing the claimed invention would have required undue experimentation. The '701

publication can not be relied upon to overcome this portion of the enablement rejection because it is Applicants own post filing date publication and as discussed above a declaration has not been filed. For these reasons the enablement rejection is maintained.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda M. Shaw/
Examiner 1634

/Stephen Kapushoc/
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